Muscle Blood-Flow Dynamics at Exercise Onset: Do The Limbs Differ?

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ABSTRACT

TSCHAKOVSKY, M. E., N. R. SAUNDERS, K. A. WEBB, and D. E. O’DONNELL. Muscle Blood-Flow Dynamics at Exercise Onset: Do The Limbs Differ? Med. Sci. Sports Exerc., Vol. 38, No. 10, pp. 1811–1818, 2006. Common approaches to understanding control of muscle blood flow in exercise focus on the contributions of various putative vasoregulatory mechanisms to the magnitude of the steady-state response. The application of systems-control principles offers a unique approach to characterizing and quantifying the non–steady-state adaptation of muscle blood flow with exercise onset. Information gained from this approach provides novel insight into the nature of control mechanisms governing physiological responses to exercise. This review is intended to provide the reader with an understanding of 1) exercise models, methodology for measuring muscle blood flow, and analysis approaches for quantifying muscle blood-flow dynamics; 2) what is currently known about the dynamic response of muscle blood-flow control mechanisms in humans; and 3) the similarities and differences in exercising muscle blood-flow control in the upper versus the lower limbs in humans. Key Words: VASODILATION, MUSCLE PUMP, KINETICS, DOPPLER ULTRASOUND, HUMAN, AGING

At the onset of exercise, muscle blood flow (and therefore oxygen delivery) increases to meet the metabolic demand of contracting muscle. Because oxygen delivery can have a profound effect on muscle metabolism and function (13,49), it has been of considerable interest to understand the nature of vascular control mechanisms responsible for matching muscle blood flow to muscle metabolic demand. A common approach has been to examine the contribution of various putative vasodilators on the steady-state response (5).

Another approach is to investigate the dynamic response of muscle blood flow to step transitions in exercise intensity (33–35). Figure 1 illustrates the typically biphasic dynamic response of muscle blood flow in a transition from rest to moderate-intensity exercise in humans. Quantification of the dynamic response characteristics of any physiological regulatory system provides unique insight into underlying mechanisms not obtainable through examination of the steady state (1,2,14,16,19). This approach includes 1) quantifying the three parameters of a dynamic response, that is, the time delay from onset of stimulus to onset of response, the time constant (rate of adaptation) of the response, and the gain (magnitude of the response); and 2) determining the number of distinct phases of a response.

This article will briefly present current exercise models and data acquisition and analysis techniques for evaluation of muscle blood-flow dynamics at exercise onset; 2) summarize what is known about exercising muscle blood-flow dynamics based on the forearm exercise model; and compare and provide an interpretation of data on the dynamic response of muscle blood flow at exercise onset in the forearm versus the leg.

EXPERIMENTAL MODELS FOR INVESTIGATING MUSCLE BLOOD-FLOW DYNAMICS

Quantification of the dynamic characteristics of muscle blood flow at exercise onset requires high temporal resolution to have a density of data in the time domain that is adequate for estimation of dynamic response parameters (19). The only technique capable of adequate resolution is Doppler ultrasound. The application of this technique in humans requires positioning of an ultrasound probe on the skin above the major artery supplying the exercising muscle mass of interest. Two measurements are required for quantification of limb blood flow. One is a measurement of vessel cross-sectional area. To obtain this, high-frequency (MHz) sound penetrates the skin and is reflected from tissue structures, allowing the “visualization” of the artery and the measurement of its diameter (Echo ultrasonography).

The second measurement is of blood-flow velocity. For this, a separate ultrasound beam is directed to intersect the artery at an angle and is reflected by the moving red blood cells. The reflected sound is shifted in frequency in proportion to the velocity of the red blood cells (“Doppler” shift) and in proportion to how “head on” the intersection of the ultrasound is with the direction of flow (this is termed the angle of insonation). This frequency shift therefore can be converted to units of flow velocity.

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Because the ultrasound beam is essentially “aimed” at the artery of interest from a remote site (surface of the skin), this technique is prone to motion artifact, whereby changes in the position of the artery relative to the ultrasound probe result in the ultrasound beam “missing” the artery and a loss of measurement of blood-flow velocity. For this reason, Doppler ultrasound cannot be used to measure exercising limb blood flow during locomotion or cycling in humans. There are two exercise models that minimize this motion artifact and allow accurate, reproducible measurements of blood flow in either the forearm or the leg. One is the forearm handgrip exercise model, in which the brachial artery above the elbow is insonated (17,34,38,40,41,43). The other model is seated single-leg knee extension (7,27,28) or two-legged knee extension/flexion (20), in which the common femoral artery is insonated.

An additional challenge facing investigators is the variability in the blood flow across the cardiac cycle and between cardiac cycles, which is attributable to the influence of muscle contraction. Figure 2 demonstrates this effect and the common approach currently used to overcome this challenge. Averaging over a complete contraction/relaxation cycle and then across multiple repeats of the step increase in exercise results in substantial minimization of the temporal variability, such that the underlying dynamics are clear enough to be quantified.

Recently, Ferriera et al. (10) have published an analysis approach that uses frequency domain assessment to eliminate the higher-frequency oscillations in blood flow attributable to the cardiac cycle and muscle contraction/relaxation effects. This technique allows the underlying response kinetics to be quantified from a single bout of exercise.

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FIGURE 2—A. Instantaneous mean blood-flow velocity of arterial inflow to muscle. Dotted line represents zero flow. Velocity below this line represents retrograde flow. Flow is pulsatile with each cardiac cycle. At the onset of exercise, the mechanical impedance of muscle contraction to arterial inflow becomes evident, as does the immediate increase in blood flow with the first relaxation. The steady-state tracing illustrates the difference in arterial inflow during relaxation (B) vs contraction (C). Arrows pointing to panel B indicate which part of the beat-by-beat quantified blood-flow velocity reflects these tracings. B. Each data point represents the blood-flow velocity averaged for a complete cardiac cycle. The beat-by-beat variability of muscle blood flow is minimal at rest but becomes quite dramatic with exercise. The lowest values reflect cardiac cycles occurring completely within contraction, and the highest values reflect cardiac cycles occurring completely during relaxation. The overlap of a cardiac cycle across contraction and relaxation cycles to varying degrees results in a range of blood-flow velocity between these two extremes. In this form, the dynamic response characteristics of muscle blood flow cannot be quantified. C. By averaging across a contraction/relaxation phase (duty cycle) and then across multiple trials, the variability is dramatically reduced, allowing the data to be fit with an exponential model whose parameters quantify the dynamics of the response.
also substantially improves the confidence interval for estimation of the parameters defining the dynamic response. However, these authors also noted that blood-flow response kinetics varied substantially from trial to trial within an individual. They conclude that averaging of response dynamics from multiple trials may still be necessary to obtain the true physiological response for a given individual.

Conduit artery blood flow represents bulk blood flow to an exercising limb. This means it includes blood flow through skin and “nonnutritive” (4) (i.e., tendon, connective tissue, and intramuscular fat tissue) vascular beds. Therefore, measurement of conduit artery flow cannot “isolate” exercising muscle blood flow. This means that issues of flow distribution within the exercising muscle, between exercising muscle and skin, and between exercising muscle and non-nutritive tissue need to be acknowledged. Cooling of the skin can be employed in some instances (43) to minimize changes in limb blood flow directed to the skin. Although nonnutritive pathways exist, the magnitude of change in flow through these pathways with the onset of exercise is currently not clear (4) and is likely minimal.

Figure 3 is a schematic of the exponential model used to quantify the dynamic response characteristics of muscle blood flow or vascular conductance. With regard to vascular conductance, which is calculated from blood flow and arterial pressure measurements, during exercise, the effect of muscle contractions on the vascular bed require acknowledgement of a “virtual” conductance. This is because in addition to the caliber of resistance vessels, the flow impedance during muscle contraction and the potential flow-enhancement effects of venous emptying (46) are at work. Typically, the response is characterized by an early rapid phase that plateaus within 5–7 s (phase I), followed by a second, slower phase beginning at 15–25 s and progressing to steady state in moderate exercise intensity (phase II) (34,39). In heavier exercise intensities, a third, very slow phase (phase III) can be detected with varied time of onset (34).

Dynamic response characteristics confer information on characteristics of the underlying control system and its mechanisms. Two characteristics of a control system of particular interest are whether it exhibits dynamic linearity and/or is first, second, or third order. Dynamic linearity is specifically related to the time constant (τ) (Fig. 3). If a blood-flow control system demonstrates dynamic linearity, the time constant of the response would be consistent across different magnitudes or intervals of the exercise-intensity change (19). Such an observation suggests that control mechanisms contributing to the response are consistent across different work-rate increases (14,21,22). The time delay also reflects a temporal (dynamic) characteristic of the response, potentially indicating the “sluggishness” of onset of control mechanisms. The number of phases of a response identify distinct sets of control mechanisms that are initiated at different times and responsible for specific portions of the total amplitude of the response. First, second, and third order refer to the number of phases of a response.

**WHAT DO MUSCLE BLOOD-FLOW DYNAMICS TELL US ABOUT CONTROL MECHANISMS IN EXERCISE HYPEREMIA?**

Numerous studies have measured muscle blood-flow adaptation at the onset of a step increase in exercise intensity. These include, but are not limited to, the following studies in forearm (17,34,38,40,41,43) and leg (18,20,28). Unfortunately, only the recent study from our laboratory by Saunders et al. (34) was designed to rigorously apply an empirical model and systems-analysis techniques to examine characteristics of the dynamic response of muscle blood-flow control mechanisms at exercise onset. Additionally, these studies have primarily examined exercise intensities in the mild to moderate range. Thus, although measurement of exercising muscle blood flow during exercise transitions has been occurring for some time now, understanding of its dynamic characteristics is quite limited.

In Saunders et al. (34), exercise steps from 1) rest to 40% peak forearm vascular conductance (FVC), 2) rest to 80% peak FVC, and 3) 40 to 80% peak FVC (Fig. 4A) were used to investigate how the magnitude and interval (rest to exercise vs exercise to exercise) of the step transition impacted parameters describing dynamic response characteristics of muscle blood-flow control mechanisms. The exercise steps and parameters describing FVC dynamics from this study are shown in Figure 4.

These data can be summarized as follows. First, for both phase I and phase II mechanisms, the magnitude of contribution to the change in muscle blood flow was in proportion to the increase in exercise intensity, and this was not altered by starting from exercise versus baseline (Fig. 4B, G1 and G2). Also, the relative contribution of each phase to the response magnitude remained consistent across all transitions (Fig. 4C). Secondly, phase I mechanisms...
demonstrated dynamic linearity in transitions from rest, with slightly delayed and slower dynamics in transitions from moderate to heavy exercise (Fig. 4B, $T_1$ and $TD_1$). In contrast, phase II mechanisms demonstrate dynamic linearity across all transitions but were slightly delayed in onset for moderate to heavy exercise steps (Fig. 4B, $T_2$ and $TD_2$).

**Phase I mechanisms.** Mechanisms contributing to this phase of blood-flow adaptation must be virtually instantaneous in their initiation and fully expressed by 5–7 s, consistent with the immediacy and early plateauing of increased blood flow. The muscle pump potentially represents a mechanism with such characteristics because the pressure gradient across a muscle vascular bed is increased with the first contraction (42). It has been suggested as the exclusive contributor to phase I, partly because previously published direct observations of resistance-vessel responses to the onset of stimulated contractions or topical application of vasodilators in situ indicated a delayed onset of 5–20 s for vasodilation (6,11,26,48). However, these times of onset are not compatible with the dynamic response of muscle blood flow in humans, where there is a plateau reached at 5–7 s that is maintained until 15–25 s of exercise (34,39). In contrast, recent observations of rapid (within 1 s of contraction onset) vasodilation in situ by two independent laboratories (24,47) are consistent with the dynamics of phase I in humans. Furthermore, our laboratory has now established that in human forearm handgrip exercise, vasodilatory mechanisms and not the muscle pump are responsible for the phase I blood-flow adaptation (35,44).

From the work of Saunders et al. (34), it would appear that these vasodilatory mechanisms provide a consistent proportion of the vascular response to an increase in exercise intensity within the intensities examined. Although the total muscle blood-flow response dynamics averaged over contraction and relaxation appeared to be slightly delayed and slower, previous work in our laboratory, in which vascular conductance was assessed during relaxation between contractions, indicates that the dynamics of these
vasodilator mechanisms are just as rapid in an exercise-to-exercise transition (35). These mechanisms do not appear to be nitric oxide—or prostaglandin dependent (33,38). The immediacy of the phase I blood-flow increase also suggests that these mechanisms are likely related to muscle activation (47) and/or mechanical distortion of resistance vessels with contraction (12,44,46).

**Phase II mechanisms.** The mechanisms responsible for the second phase of muscle blood-flow adaptation are delayed in onset and slower in response adaptation than those for phase I. Types of mechanisms thought to contribute to this adaptation of exercise hyperemia to steady state include 1) metabolic vasodilator accumulation, which can have direct local effects (5,50) and can also be communicated upstream via “conducted” vasodilation (6,37); 2) shear-induced vasodilation (23); and 3) red blood cell de-oxygenation, which has both local and conducted vasodilatory effects (8). Mechanisms 1 and 3 are to a large degree consistent with feedback control, as reviewed by Hughson (15), in which the mismatch between metabolism and blood flow results in the interstitial accumulation of vasodilators, which increase blood flow until a balance between production and removal of these dilators is established. Although numerous vasodilator candidates have been identified (5), it is clear that there is redundancy and synergy of mechanisms, such that no single vasodilator appears to be essential for the normal adaptive response of blood flow. Thus, dynamics of muscle blood-flow adaptation characterizes the net interactive adaptation effect of multiple mechanisms.

The delay in onset and the rate of increase in smooth-muscle relaxation would reflect the interaction of accumulation to threshold levels and the turning on of the smooth-muscle signal-transduction cascade, culminating in smooth-muscle relaxation. This group of mechanisms does not accumulate to physiologically significant levels until 15–25 s after an increase in exercise intensity. The observation that the phase II time delay is greater for steps initiated from exercise versus rest is consistent with baseline blood flow or vascular tone having an impact on i) accumulation of vasodilators to levels where changes in vascular conductance are initiated, ii) threshold for increase in vasodilatory signal-transduction cascade, or both.

The observation of dynamic linearity across exercise transitions in the study of Saunders et al. (34) indicates a consistency in the rate of overall vascular bed smooth-muscle relaxation with the initiation of this set of mechanisms.

**Phase III mechanisms.** The mechanisms responsible for the third, slow phase in heavy exercise are less consistent in onset and the rate of blood-flow adaptation they incur (34) (Fig. 4B, G, T, and D). Little is known about the origin of this phase of muscle blood-flow adaptation. It may be related to the slow component of the oxygen cost in heavy exercise (29–31), either as part of the expected oxygen cost or as part of an additional cost incurred by the recruitment of less metabolically efficient type II muscle fibers as some motor units fatigue (1,32).

### ARM VERSUS LEG: DIFFERENCES IN MUSCLE BLOOD-FLOW DYNAMICS AND CONTROL MECHANISMS?

Currently, the only data in the literature that allow comparison of the dynamic characteristics of exercising muscle blood-flow control mechanisms between the arm and the leg are those of Saunders et al. (34) (forearm exercise) and MacDonald et al. (20) (leg exercise). These studies allow comparison because the relative work rates used were similar, the exponential modeling was the same, and the position of the exercising muscle mass relative to heart level was the same. We have recently completed investigations into the forearm versus leg dynamic adaptation of blood flow in patients with chronic obstructive pulmonary disease and healthy age-matched controls. Preliminary data was published in abstract form (45). This section will address the issue of limb differences based on these data. Table 1 summarizes the subject and exercise characteristics in these studies.

**Forearm versus Legs in Young Healthy Subjects**

Figure 5 provides a graphic and numeric comparison of the dynamic response of muscle blood-flow control mechanisms.
at the onset of exercise in the forearm and the legs of young healthy humans. A statistical comparison between the data sets was not possible.

**Phase I mechanisms.** There is no difference of physiological significance in the mean values for parameters describing the phase I (Fig. 5); despite a lack of statistical comparison, it appears safe to conclude that in young healthy humans, rapidly acting mechanisms initiating muscle blood-flow responses to exercise in the forearm and legs appear to be similar in terms of their dynamic characteristics. Less clear is whether the relative contributions to the total response magnitude is different between limbs.

**Phase II mechanisms.** The delay in onset of phase II mechanisms is virtually identical between limbs. This may suggest that “threshold” changes in metabolic vasodilator accumulation or red blood cell deoxygenation effects on vascular smooth muscle are the same. However, there appears to be a considerably faster adjustment in vascular conductance to steady state in the forearm. It is unlikely that this indicates fundamentally different vasodilatory mechanisms at work. It is more likely that the same mechanisms have faster response characteristics. A potential hypothesis for this phenomenon comes from the recent data from Newcomer et al. (25) on dose-response “sensitivity” of forearm versus leg resistance vessels. Their data indicate that the vascular conductance response across a number of doses of acetylcholine, substance P (both endothelium dependent), and sodium nitroprusside (endothelium independent) is greater in the forearm than in the leg. It is plausible that in the forearm, the greater increase in blood flow at a given time in phase II for a given amount of vasodilator, reflected by a faster \( \tau \), could be explained in part by the findings of Newcomer et al. (25). If other vasodilatory mechanisms contributing to this phase demonstrate similar limb dose-response differences, this may explain why the forearm adjusts muscle blood flow more rapidly than the leg.

Another possibility relates to the phenomenon of conducted vasodilation. It is becoming clear that communication of local metabolic demand upstream to feed arteries is essential for achieving adequate increases in vascular conductance (3, 9, 36). Although no studies to date have compared the speed of conducted vasodilation across different muscles, there may be differences in the speed of conducted vasodilation in the forearm versus the legs of young healthy humans. This may also be a “scaling” issue, in that the size of the muscle determines the length of the vascular bed along which these conducting signals must travel. These hypotheses remain to be tested.

**FOREARM VERSUS LEG: CHANGES WITH AGE AND COPD**

Figures 6 and 7 provide graphic and numeric comparisons of the dynamic responses of muscle blood-flow control mechanisms at the onset of exercise in the forearm and the legs of older healthy and COPD subjects, respectively.

**Phase I mechanisms**

The dynamic characteristics of phase I mechanisms appear to be preserved with age and COPD (i.e., no difference in a
statistical comparison with the young healthy individuals was evident) (34,45). However, the relative contribution to the total response magnitude was significantly blunted with age and further with COPD in the forearm but not in the leg (see Figs. 5–7 within limbs). Thus, there does appear to be a sensitivity of these mechanisms to aging and to COPD in the forearm that was not apparent in the legs.

Phase II mechanisms

A comparison within limbs across Figures 5–7 reveals the effect of aging and COPD on this set of mechanisms. First, the delay in onset of effect of these mechanisms appears remarkably insensitive to age and COPD, despite the observation that the magnitude of blood-flow adaptation achieved in phase I is progressively blunted across these groups. However, a limb-specific effect of aging on the rate of adaptation in blood flow is clearly accomplished by this set of mechanisms. In essence, these mechanisms seem to become “slower” in the arm so that the arm is the same as the leg in the older subjects. There is no further slowing, however, with COPD.

There are two possible explanations for this. First, if the hypothesis that the rate of adaptation of phase II reflects sensitivity of vascular smooth muscle to vasodilatory mechanisms is correct, then a reduction in that sensitivity with aging in the forearm but not in the leg would result in slowing of arm phase II but not leg phase II. Second, it has recently been demonstrated in mouse muscle that, although the steady-state vasodilation in contracting skeletal muscle of mice is preserved with aging, the propagation of conducted vasodilation for a given local application of acetylcholine is blunted (3). Little is known about factors that affect conducted vasodilation, but it is possible that conducted vasodilation in the forearm but not the leg is blunted with age.

SUMMARY AND CONCLUSIONS

This paper presents the first examination of limb-specific vascular control as assessed by dynamic response characteristics. The paucity of data in the literature regarding dynamic characteristics of vasodilatory mechanisms and muscle blood-flow responses to exercise mean that it is at present not possible to paint a detailed picture of similarities/differences in dynamic characteristics of vascular control mechanisms in exercise between limbs.

Preliminary findings indicate that the major characteristics differentiating the limbs reflect a sensitivity of the forearm vasculature to aging and COPD that is not demonstrated by the leg vasculature. In essence, although the phase II mechanisms in the forearm are faster than in the legs in young healthy persons, these mechanisms slow with age. Furthermore, phase I mechanism contributions to exercise hyperemia are blunted with age and with COPD in the forearm but are preserved in the legs.

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